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# Outcome of 67 Patients With Hepatocellular Cancer Detected During Screening of 1125 Patients With Chronic Hepatitis

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## Objective

We performed this prospective screening trial in chronic hepatitis virus-infected patients to determine the incidence of hepatocellular cancer (HCC) and the resectability and long-term survival rates of these HCC patients.

## Summary Background Data

Chronic hepatitis B or C virus infection is a major etiologic factor in human HCC. It is not clear if routine screening of chronic viral hepatitis patients improves the survival of patients who develop HCC.

## Methods

Screening for HCC was offered to patients chronically seropositive (>5 years) for hepatitis B or C infection. All patients underwent percutaneous core liver biopsy to assess the histologic severity of chronic liver injury. Patients were screened initially and every 3 months thereafter with serum alpha-fetoprotein and transabdominal ultrasound evaluations; HCC was confirmed by needle biopsy of liver tumors.

## Results

Screening was performed on 1125 hepatitis-positive patients (804 with hepatitis C, 290 with hepatitis B, 31 with both). On liver biopsy, 800 patients had mild chronic active hepatitis and 325 had severe chronic active hepatitis, cirrhosis, or both. Initial screening detected HCC in 61 patients. HCC was detected in six more patients during follow-up; thus, the incidence of HCC was 5.9% (67/1125). However, 66 of the 67 HCC cases (98.5%) arose in the 325 patients with severe chronic active hepatitis or cirrhosis (66/325 [20.3%] *vs.* 1/800 [0.1%], $p < 0.0001$ [Wilcoxon signed rank]). Median follow-up of the 67 HCC patients was 24 months. Locally advanced or metastatic, unresectable HCC occurred in 43 patients (64.2%); 24 patients (35.8%), including the 6 patients detected during follow-up screening, underwent margin-negative resection. The median survival for the 24 resected patients was 26 months, compared to 6 months for the 43 patients with unresectable cancer ($p < 0.0001$, Wilcoxon signed rank).

## Conclusions

HCC was found to arise in 20.3% of patients with chronic hepatitis B or C infection and severe liver injury. Initial screening detected resectable lesions in less than half the HCC patients. Routine screening of chronic hepatitis B or C virus-infected patients with ultrasound and alpha-fetoprotein determination should be reserved for patients with severe chronic active hepatitis, cirrhosis, or both.

In a 1996 report to the Italian Ministry of Health, hepatocellular cancer (HCC) was noted to be the third most common gastrointestinal malignancy affecting men and women in the Campania region of Italy.[1] This report also noted that HCC occurs at a much higher frequency in Campania than in most other regions of Italy; in Campania, HCC is the seventh most common cause of cancer-related death in men and women. The relatively higher incidence of HCC in Campania corresponds to a high rate of chronic hepatitis virus infection, particularly hepatitis C virus. Chronic hepatitis B or C virus infection is a major etiologic factor in human HCC. The high incidence of chronic viral hepatitis and HCC in the Campania region led to our initiating, in 1993, a prospective clinical screening program for HCC arising in chronic viral hepatitis patients.

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**Figure 1.** The Campania region of Italy. Naples and Salerno are the two largest cities in the region. The estimated population of the region is 5.2 million.

We previously reported 36 cases of asymptomatic HCC detected during screening in the first 416 patients entered in this study.[2] Interestingly, 35 of these 36 cases of HCC occurred in a subset of 140 patients with liver biopsies showing severe chronic active hepatitis, cirrhosis, or both, representing a 25% incidence of HCC in this group of patients with histologically severe liver injury. We have now completed screening and data analysis on a larger group of chronic viral hepatitis patients to confirm the high incidence of HCC in patients with histologically severe liver injury and to determine the resectability and long-term survival rates of these HCC patients detected during prospective screening.

## METHODS

This study was conducted from July 1, 1993, through June 30, 1996. Patients from the Campania region of Italy (Fig. 1) who were seropositive for viral hepatitis infections were registered and followed at designated district hospitals. All patients with chronic hepatitis B or C virus infections of at least 5 years' duration were offered a screening program to detect HCC at the G. Pascale National Cancer Institute in Naples. Chronic hepatitis B virus infection was defined as persistently positive sera for hepatitis B surface antigen, as determined by reverse passive hemagglutination on three or more blood samples drawn at 3-month intervals. Chronic hepatitis C virus infection was defined as persistently positive sera for hepatitis C virus on first- and second-generation antihepatitis C virus enzyme- linked immunoassays on three or more blood samples drawn at 3-month intervals. Patients with Child class B or C cirrhosis, a history of hepatic encephalopathy, bleeding gastroesophageal varices, ascites, or a prior diagnosis of any type of malignancy were excluded from the study.

All patients underwent outpatient physical examination, abdominal ultrasonography, serum liver function tests (direct and indirect bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, albumin, prothrombin time), and serum alpha-fetoprotein (AFP) measurements at entry and at 3-month intervals thereafter. When a mass lesion in the liver was detected by ultrasonography or when the serum AFP level exceeded 10 ng/mL, further diagnostic evaluation was performed with intravenous bolus contrast computed tomography (CT) scans and magnetic resonance imaging (MRI) of the abdomen. Confirmed liver tumors were biopsied under ultrasound or CT guidance, and the histologic diagnosis of HCC was based on routine hematoxylin and eosin staining.

At the time of entry in this study, all patients underwent a percutaneous core liver biopsy to determine the histologic severity of chronic liver injury. Histopathologic diagnostic criteria were based on the European classification system.[3] Based on the histopathologic findings from the liver biopsies, patients were classified as having chronic persistent hepatitis, mild chronic active hepatitis, severe chronic active hepatitis, or cirrhosis with or without chronic active hepatitis (all Child class A).

Patients diagnosed with HCC underwent further clinical evaluation with a chest radiograph and serum laboratory tests (complete blood count, platelet count, blood urea nitrogen, creatinine, glucose, and electrolytes). Chest CT scan was performed if there was a question of lung metastases. Patients diagnosed on clinical and radiographic examination with only a solitary liver lesion judged to be resectable (a resection leaving adequate functional hepatic parenchyma) underwent exploratory laparotomy and intraoperative ultrasound. A margin-negative liver resection was performed if there was no evidence of either extrahepatic metastasis or multifocal tumor on intraoperative ultrasound. Patients with only solitary liver lesions judged to be unresectable because of tumor size or intrahepatic location were treated on protocol with percutaneous ethanol injection (PEI). Patients with multifocal liver disease or metastatic disease were treated on protocol with systemic chemotherapy. All HCC patients were followed after resection, PEI, or initiation of systemic chemotherapy every 3 months with serum AFP levels, serum liver function tests, abdominal CT scanning, and chest radiography.

Statistical analysis of data was performed using the Wilcoxon signed rank test. Actuarial survival in patients diagnosed with HCC was calculated according to the Kaplan-Meier method.

**Table 1. TRANSABDOMINAL HEPATIC ULTRASONOGRAPHY AND SERUM ALPHA FETOPROTEIN DETERMINATION TO DETECT 67 CASES OF HEPATOCELLULAR CANCER IN 1,125 PATIENTS WITH CHRONIC VIRAL HEPATITIS**

| Ultrasonography | n | % |
|---|---|---|
| Liver mass on US, elevated AFP | 41 | 61.2 |
| Liver mass on US, normal AFP | 17 | 25.4 |
| Normal US, elevated AFP | 9 | 13.4 |
| Total | 67 | 100 |

Elevated AFP = serum AFP > 10 ng/mL.
US, ultrasonography; AFP, serum alpha fetoprotein; n, number of cases.

## RESULTS

The screening program registered 1125 patients, of whom 672 were men (59.7%) and 453 were women (40.3%). The median age was 56.1 years (range 33–79 years). No patient had any clinical symptoms related to liver dysfunction or HCC. Chronic hepatitis C virus infection was confirmed in 804 patients (71.5%), chronic hepatitis B virus infection was present in 290 patients (25.8%), and 31 patients had both hepatitis B and C virus infections (2.7%). The duration of chronic hepatitis virus infection ranged from 5 to 17 years (median, 10.2 years).

At the time of initial screening, asymptomatic HCC was detected in 61 patients, yielding an initial detection rate of 5.4%. An additional six cases were diagnosed during follow-up evaluations in patients who on initial evaluation had a normal serum AFP level and no liver tumor by ultrasonography. All six of these patients developed increasing serum AFP levels 9 to 18 months after entry in the study. In four of these six patients, transabdominal ultrasonography demonstrated a solitary liver tumor <3 cm concomitant with the elevation in serum AFP level. In the remaining two patients, ultrasonography did not reveal a liver mass, but high-resolution CT scanning detected a solitary liver tumor <3 cm.

The suggestion of a diagnosis of HCC based on ultrasonography or elevated serum AFP in all 67 patients is indicated in Table 1. Ultrasonography demonstrated a liver tumor (or tumors) in 58 of the 67 patients (86.6%); the serum AFP level was elevated in 50 of the 67 HCC patients (74.6%). Overall, 67 of the 1125 chronic hepatitis virus-infected patients (5.9%) were diagnosed with HCC during this screening program.

Of the 67 patients diagnosed with HCC, 58 (86.6%) had chronic hepatitis C virus infection, 5 (7.5%) had chronic hepatitis B virus infection, and 4 (5.9%) had both hepatitis B and C virus infections. The percutaneous core liver biopsies performed on all patients entered in this screening program indicated that 800 patients (71.1%) had chronic persistent hepatitis or mild chronic active hepatitis. Thus, 325 patients (28.9%) had biopsies demonstrating severe hepatitis-related liver injury (severe chronic active hepatitis, cirrhosis, or both). Evaluation of the severity of chronic liver injury in patients who developed HCC revealed that 66 of the 67 HCC cases (98.5%) arose in the 325 patients with severe chronic active hepatitis, cirrhosis, or both. Thus, there was a marked difference in the incidence of HCC in the patients with severe chronic liver injury (66/325 [20.3%]) compared to the patients with histologically less severe chronic liver injury (1/800 [0.1%], $p < 0.0001$).

Evaluation of the extent of disease at the time of diagnosis of HCC in the 67 patients indicated that 28 patients (41.8%) had disease confined to the liver that appeared to be resectable, 14 patients (20.9%) had a solitary liver lesion judged to be unresectable (based on central location within the liver that would require a major lobar resection in patients with inadequate functional hepatic reserve or adjacency to a major intrahepatic vascular structure precluding a margin-negative resection), and 25 patients (37.3%) had multifocal hepatic tumor or extrahepatic metastatic disease. The 28 patients with apparently resectable solitary HCC underwent exploratory laparotomy. However, four of the patients were found to have extrahepatic nodal metastases and liver resection was not performed. Thus, 24 of the 28 patients who underwent surgery (85.7%) underwent a liver resection with at least a 1-cm margin of nonaffected (tumor-negative) hepatic parenchyma. There were no operative or postoperative deaths in these 24 patients. Resection was possible in only 35.8% of the entire group of 67 HCC patients. Included in the 24 patients who underwent liver resection with curative intent were the 6 patients with an initially normal ultrasound and serum AFP level whose HCC was detected during routine follow-up screening.

The 14 patients with solitary, unresectable liver tumors were treated with PEI on an active institutional protocol. All the tumors treated with PEI were <5 cm in diameter. The 29 patients (43.3%) with multifocal or metastatic HCC were treated on one of two active phase II institutional protocols. A total of 43 of the 67 HCC patients (64.2%) presented with unresectable disease.

At the time of this report, with a median follow-up of 24 months for the 67 HCC patients, all 29 patients with multifocal or metastatic HCC had died from their disease. The median survival of the 43 patients with unresectable HCC was 6 months, compared to 26 months for the 24 patients who underwent a hepatic resection ($p < 0.0001$). Of the 14 patients treated with PEI, 9 had died of their disease, 2 were alive with disease, and 3 were alive without evidence of recurrent HCC more than 2 years after treatment. Of the 24 resected patients, 8 had died of recurrent HCC, 1 was alive with a hepatic recurrence of HCC, and 15 were alive without evidence of recurrent HCC. The 5-year actuarial survival curves for the 67 HCC patients are shown in Figure 2.

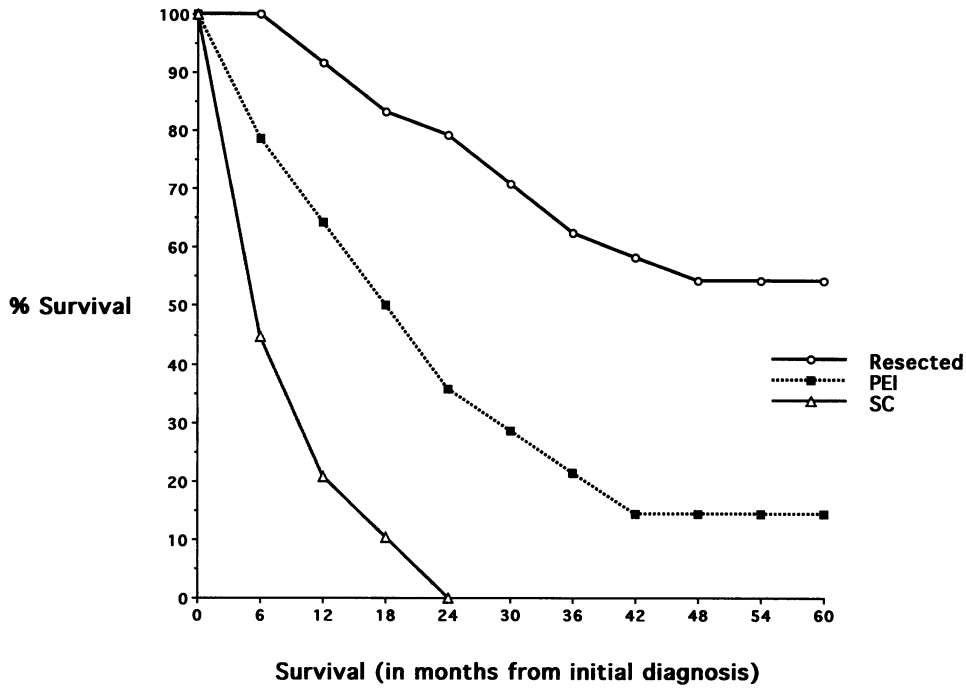


**Figure 2.** Five-year actuarial survival curves for 67 hepatocellular cancer (HCC) patients. All 67 patients were asymptomatic, and HCC was diagnosed during a screening program in 1125 chronic hepatitis B or C virus-infected patients. Screening was performed with transabdominal ultrasonography and serum alpha-fetoprotein measurement. The 5-year actuarial survival rate for the 24 resected patients (Resected) was significantly greater than for the group treated with percutaneous ethanol injection (PEI, n = 14) or systemic chemotherapy (SC, n = 29) by the Wilcoxon signed rank test ($p < 0.001$).

## DISCUSSION

In high-incidence regions, the chance of developing HCC is 160 times greater in hepatitis B virus carriers than in persons not infected with hepatitis B virus.[4] It is chronic infection, also known as carrier status, with hepatitis B virus that imparts the high risk for HCC. Patients who are chronically positive on serum analysis for hepatitis B surface antigen have a 200-fold increased risk of developing HCC when compared with patients who are not chronic carriers after hepatitis B virus infection.[5] Only 5% to 10% of hepatitis B virus infections result in chronic infection, whereas most hepatitis C virus infections result in a carrier state. Although the hepatitis C virus is molecularly unrelated to the hepatitis B virus, infection with either virus increases the risk of developing HCC. An epidemiologic study of 62,280 Japanese suggests that 28% of male and 6% of female hepatitis C virus carriers will develop HCC.[6] Another study reporting 180 chronic hepatitis B virus-positive and 349 chronic hepatitis C virus-positive patients revealed 5-, 10-, and 15-year HCC appearance rates of 14.2%, 27.2%, and 27.2%, respectively, in hepatitis B virus patients, compared with much higher rates of 21.5%, 53.2%, and 75.2%, respectively, in chronic hepatitis C virus patients.[7] Because patients chronically infected with hepatitis B or C virus are at increased risk of developing HCC, it is important to determine if screening programs are cost-effective and accurate in detecting HCC at a potentially curable stage of disease.

Studies from areas of the world with a moderate to high incidence of HCC have indicated that real-time transabdominal ultrasonography combined with serum AFP determination is an accurate and relatively inexpensive method to screen chronically infected hepatitis B or C virus patients.[8–12] Our results are consistent with the finding in these studies that ultrasonography detects asymptomatic HCC more frequently than serum AFP determination.

Using only serum AFP measurements to screen high-risk patients for HCC is associated with two problems. First, transient increases in serum AFP levels may occur in benign chronic liver disease, especially during exacerbations of hepatitis.[13] In healthy adults not infected with hepatitis virus, serum AFP concentrations are <5 ng/mL. During acute exacerbations of hepatitis in chronically infected patients, almost 10% of patients have a transient increase in serum AFP levels to >100 ng/mL. The second problem is that when considering all patients diagnosed with HCC, only two thirds have elevated serum AFP levels.[14] In patients with a solitary HCC <5 cm in diameter, 40% have serum AFP levels <20 ng/mL.[15] Serum AFP levels do not correlate with the size of the primary HCC, the extent of intrahepatic disease, or the presence of extrahepatic metastases. Very well-differentiated or extremely anaplastic HCC

is usually associated with minimal or no elevation of serum AFP levels.[16]

Most reports indicate that ultrasonography detects HCC <3 cm in diameter with greater accuracy than serum AFP determination, but in two of our six patients who were detected during follow-up evaluation, the diagnosis was suggested by a rising serum AFP level alone. High-resolution CT scans were necessary to confirm the small liver tumors in these two patients with a normal ultrasound examination of the liver. Diagnostic accuracy in detecting early-stage HCC is improved using high-resolution abdominal CT scans, CT angioportography, and MRI in patients with borderline ultrasonography findings or AFP elevations.[12]

Screening high-risk populations with ultrasonography and serum AFP levels leads to a diagnosis of resectable HCC in 40% to 60% of the HCC patients.[9–12] In our study, 61 patients were diagnosed with HCC at the time of their initial screening with ultrasonography and serum AFP level measurement. Only 18 of these patients (29.5%) were detected at an early stage of disease where resection was possible. However, six additional patients were diagnosed with HCC during follow-up testing subsequent to their initial negative screening evaluation, so 24 of the 67 HCC patients (35.8%) were detected with resectable lesions. This latter group of six patients underscores the importance of longitudinal screening in high-risk patient populations.

There is a clear improvement in the long-term survival of patients undergoing resection when HCC is diagnosed while the tumor is solitary and <5 cm in diameter. A number of studies have demonstrated that patients diagnosed with small, solitary, asymptomatic HCC have significantly higher 3- and 5-year survival rates than patients with large, multicentric, or symptomatic HCC.[17–22] The 5-year actuarial survival in our 24 patients who underwent a margin-negative resection is 54.2%, consistent with the 45% to 60% 5-year survival rates reported after resection of a small, asymptomatic HCC. In contrast, resection of HCC when symptomatic or >5 cm in diameter produces 5-year survival rates of 25% or less.[20]

Even when HCC is diagnosed and resected when the tumor is solitary, <5 cm in diameter, and asymptomatic, a significant proportion of the patients still die of recurrent disease. After a margin-negative liver resection, 9 of our 24 resected HCC patients (37.5%) developed hepatic recurrence of HCC. Although some of these nine patients also developed distant metastatic disease, it was the recurrent liver disease and subsequent liver dysfunction that determined their survival.

Patients with HCC arising in a liver affected by severe chronic active hepatitis, cirrhosis, or both appear to be at an increased risk for hepatic recurrence of HCC after resection because of metachronous multicentric carcinogenesis.[21,22] A recent study indicates that after resection of HCC, the recurrence-free survival rate in patients with normal hepatic parenchyma or chronic persistent hepatitis is significantly greater than that for patients with severe chronic active hepatitis, cirrhosis, or both.[23] The 5-year recurrence-free survival rate for patients with chronic persistent hepatitis was almost 90%, whereas the 5-year recurrence-free survival rates for patients with cirrhosis and patients with severe chronic active hepatitis were 35% and 10%, respectively. Patients with severe chronic active hepatitis or cirrhosis frequently develop recurrence after resection in the opposite lobe or in both lobes; the recurrences often develop at multiple sites in the liver.[23] This study supports the suggestion that field cancerization throughout the liver is a significant cause of hepatic recurrence of HCC in patients with hepatitis virus-related severe histologic injury. Clearly, further improvements in survival after resection of small, asymptomatic HCC in patients with severe chronic active hepatitis or cirrhosis will require multimodal adjuvant therapies that limit and possibly reverse the ongoing chronic liver injury.

In an era of spiraling costs and limited public and private resources to pay for health care, the issue of cost-effectiveness for any long- term screening program is cogent. The issue of the cost-effectiveness of screening to detect small HCC in patients with Child class A cirrhosis was addressed in a recent paper that drew data from the medical literature.[24] The authors developed a decision analysis model representing the natural history of cirrhosis and risk for developing HCC and compared a strategy of performing transabdominal ultrasonography and serum AFP measurement every 6 months with a strategy of seeking tumors only if clinically symptomatic. For both strategies, a partial hepatectomy was performed for the predicted patients with resectable disease. Within the constraints of their model, the cost-effectiveness ratios to increase life expectancy for patients with HCC detected on routine screening ranged between $26,000 and $55,000 for each additional life-year gained. The model assumed that at least 60 screening procedures would be necessary to detect one case of HCC amenable to surgery. If viewed in the entire context of our 1125 patients who underwent screening, our detection rate was one resectable HCC for every 47 patients screened. However, this number is also not an accurate representation, because the 24 patients with resectable HCC in our study were in the group of 325 patients with severe histologic injury related to chronic hepatitis virus infection. In this high-risk group, the rate of detection of resectable HCC was one in every 13.5 patients.

Thus, the results in our patients do not support the assumptions of the hypothetical model or the resultant suggestion that screening of high- risk chronic hepatitis patients is not cost-effective. Instead, our results support screening programs for properly selected patients in a group with a greater than 20% overall incidence of HCC.

Obviously, it is important to define as precisely as possible the group of patients who are at highest risk to develop any given disease entity. We used an older classification system for the severity of chronic hepatitis virus-related

liver injury. It is possible that with the use of recently advocated expanded systems of histologic classification of chronic hepatitis or through the development of better molecular markers predicting the development of HCC, we will refine the decision-making process to place the appropriate chronic hepatitis patients in long-term HCC screening programs.[25] Until that time, we believe that patients with histologically severe liver injury from chronic hepatitis virus infection should be screened every 6 months with transabdominal ultrasonography and serum AFP determination. Chronic hepatitis patients with minimal liver injury are less likely to benefit from long-term screening programs and with a low risk of developing HCC should be followed clinically.

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